Multidrug-Resistant *Neisseria gonorrhoeae* with Decreased Susceptibility to Cefixime—Hawaii, 2001

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We report 4 urogenital *Neisseria gonorrhoeae* isolates recovered from 3 patients that demonstrated resistance to penicillin, tetracycline, and ciprofloxacin and reduced susceptibility to cefixime. This report of the first 3 patients in the United States identified with this multidrug-resistant strain may portend an emerging problem for clinicians and public health officials.

Neisseria gonorrhoeae infects ~800,000 people in the United States annually [1, 2] and most commonly causes urethritis, cervicitis, and pharyngitis. Significant complications resulting from gonorrhea include pelvic inflammatory disease, ectopic pregnancy, and infertility. Gonococcal infection also increases the risk of HIV transmission by 3–5-fold [3, 4]. Over the years, the ability of *N. gonorrhoeae* to readily acquire antimicrobial resistance to a variety of agents, especially penicillin, tetracycline, and ciprofloxacin, has complicated the treatment and control of gonorrhea. Third-generation cephalosporins, such as ceftriaxone and cefixime, have been important, reliable therapeutic options in places with increasing prevalence of fluoroquinolone-resistant *N. gonorrhoeae.* We report a cluster of multidrug resistant *N. gonorrhoeae* infections that had decreased susceptibility to cefixime, which is the first identification of such strains in the United States.

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Case reports. In February 2001, patient A, a 35-year-old white man residing in Hawaii, presented to the STD clinic with a 3-day history of dysuria and a yellow-white urethral discharge that contained gram-negative intracellular diplococci. Patient A was treated for gonorrhea with cefixime (400 mg po) and for possible *Chlamydia trachomatis* infection with azithromycin (1 g po). Culture of urethral discharge grew *N. gonorrhoeae* that was resistant to penicillin, tetracycline, and ciprofloxacin and exhibited decreased susceptibility to cefixime (table 1). Patient A returned in April 2001 and reported having had persistent symptoms of urethritis. He was treated with spectinomycin (2 g im) and a 7-day course of doxycycline (100 mg b.i.d. po). A second culture of urethral discharge grew *N. gonorrhoeae* with a similar antibiogram as the first isolate. Three weeks later, the patient reported complete symptom resolution, and a test-of-cure culture showed no growth. Patient A reported having 2 female sex partners, both of whom visited Hawaii from Japan.

One of patient A's sex partners, a Japanese tour guide, could not be located; the second, patient B, presented in May 2001. Patient B was a 27-year-old Japanese female visitor to Hawaii who reported having had yellow vaginal discharge since February 2001, having had only Patient A as a sex partner, and having had sex with him once in February 2001 (before his first clinic visit) and once in April 2001 (before his second clinic visit). She was treated with ceftriaxone (125 mg im) and azithromycin (1 g po). Culture of endocervical samples grew *N. gonorrhoeae* with an antibiogram that matched that of the isolate recovered from patient A (table 1). However, the isolate recovered from patient B had an MIC of cefixime of 0.25 mg/L, which is cefixime susceptible, according to NCCLS criteria [5], but which is also within only 1 dilution of 0.5 mg/L, the cefixime-susceptibility breakpoint.

Patient C was a 30-year-old Micronesian man residing in Hawaii who presented in March 2001 with a 4-day history of dysuria and yellow urethral discharge that contained gram-negative intracellular diplococci. Patient C was treated with cefixime (400 mg po) and azithromycin (1 g po). Culture of urethral discharge grew *N. gonorrhoeae* resistant to penicillin, tetracycline, and ciprofloxacin, and with decreased susceptibility to cefixime. Results of a test-of-cure performed 3 months later were negative for *N. gonorrhoeae,* and the patient reported complete symptom resolution. Patient C reported having 1 female sex partner who lived in Hawaii but who was originally from Malaysia or the Marshall Islands and could not be located.

The 4 isolates from patients A–C were strain-typed and found

Table 1. Antimicrobial susceptibilities, as determined by the agar dilution method, for *Neisseria gonorrhoeae* isolates from patients A–C.

Isolate source, date recovered	β-lactamase	Antimicrobial						
		Penicillin	Tetracycline	Spectinomycin	Cefixime	Ceftriaxone	Ciprofloxacin	Azithromycin
Patient A, Feb 2001	Negative	8.0	8.0	Susceptible	0.5	0.125	8.0	0.25
Patient A, Apr 2001	Negative	8.0	4.0	Susceptible	0.5	0.125	8.0	0.125
Patient B, May 2001	Negative	8.0	4.0	Susceptible	0.25	0.125	16.0	0.125
Patient C, Mar 2001	Negative	8.0	8.0	Susceptible	0.5	0.125	8.0	0.125

NOTE. Data are MICs in mg/L, unless otherwise indicated. Tests were performed at the Seattle Gonococcal Isolate Surveillance Project (GISP) Regional Laboratory. Isolates were retested at the Centers for Disease Control and Prevention, and the MICs were consistent with results from the Seattle GISP Regional Laboratory. NCCLS criteria for antimicrobial resistance in *N. gonorrhoeae* are as follows: MIC of penicillin, ⩾2.0 mg/L; tetracycline, ⩾2.0 mg/L; spectinomycin, ⩾128.0 mg/L; and ciprofloxacin, ⩾1.0 mg/L [6]. NCCLS criteria for resistance to ceftriaxone, cefixime, and azithromycin have not been established for *N. gonorrhoeae,* but NCCLS susceptibility criteria for the 2 cephalosporins for *N. gonorrhoeae* are MIC of ceftriaxone, ⩽0.25 mg/L, and MIC of cefixime, ⩽0.25 mg/L.

to be identical to each other. All 4 isolates had the same auxotype [6], lipoprotein strain type [7], and alterations in the *gyrA* and *parC* genes [8]; specifically, all were proline-requiring protein IB with lipoprotein 17c and 91,95 (→glycine), serine 87 (→arginine).

Discussion. These first US reports of multidrug-resistant *N. gonorrhoeae* with decreased susceptibility to cefixime are of concern because the spread of such strains threatens to further limit treatment options for gonorrhea. The Centers for Disease Control and Prevention (CDC; Atlanta, GA)–recommended treatments for uncomplicated gonococcal infections in much of the United States are single-dose regimens of cefixime (400 mg) or ceftriaxone (125 mg) or a fluoroquinolone (e.g., ciprofloxacin [500 mg], ofloxacin [400 mg], or levofloxacin [250 mg]) [9]. Prevalence of fluoroquinolone resistance among *N. gonorrhoeae* isolates in Asian countries in 2001 was reported to be 86.9% in China, 64.0% in Japan, and 54.3% in the Philippines [10]. In recent years, the prevalence of fluoroquinolone resistance among *N. gonorrhoeae* isolates in Hawaii has increased rapidly, from 1.4% in 1997 to 10.4% in 2000 and 19.7% in 2001 [11–13]. Fluoroquinolone resistance among isolates from California increased from 0.6% in 1999 to 2.7% in 2001, with a prevalence of nearly 5.0% in the last 6 months of 2001 [12, 13]. As a result, the CDC and other public health agencies do not recommend using quinolones to treat gonorrhea, if patients or their sex partners are likely to have acquired their gonococcal infections in Asia, the Pacific Islands, Hawaii, or California [9, 11, 13]. Cefixime and ceftriaxone are, therefore, the primary effective therapeutic options to treat gonorrhea in many areas of the world. Spectinomycin is also a useful alternative for the treatment of uncomplicated urogenital and anorectal gonorrhea, but it is not sufficiently effective for treating pharyngeal gonorrhea [14].

Two of the patients, A and C, were treated with cefixime. Although patient C apparently was successfully treated, it was unclear whether patient A experienced treatment failure. He received diagnoses of identical gonococcal infections in February 2001 and April 2001 and reported persistent symptoms during the interval, despite receipt of cefixime and azithromycin treatment in February. Cefixime treatment failures have not been documented for gonorrhea in the United States, but isolates with MICs of cefixime of >0.125 mg/L have also not been common enough to assess cefixime treatment success for infections with higher MICs. One issue is whether the azithromycin (1 g) given as cotreatment for *C. trachomatis* infection would be expected to have successfully cured patient A's gonorrhea, even if the cefixime (400 mg) did not. However, clinical treatment failures have been reported when patients infected with gonococcal strains having MICs of azithromycin of 0.125–0.5 mg/L were treated with azithromycin (1 g) [15–18]. Because patient A's strains had such MICs of azithromycin, it is possible that neither antimicrobial agent given in February cured patient A's gonorrhea. Patient A's persistent symptoms may have been due to nongonococcal nonchlamydial urethritis, to gonococcal reinfection as a result of reexposure to an infected partner, or to cefixime gonococcal treatment failure.

These Hawaii strains were identified by means of the Gonococcal Isolate Surveillance Project (GISP), a sentinel surveillance system that was established in 1986 by the CDC, in collaboration with selected sexually transmitted disease clinics at state and local health departments, to monitor gonococcal resistance in the United States [19]. Approximately 5000 gonococcal isolates are monitored annually by the GISP. From 1992 (the first year of cefixime susceptibility testing) through 2000, <45 isolates had been found to have decreased susceptibility to cefixime. Although some of these isolates were resistant to penicillin and/or tetracycline, none were also resistant to fluoroquinolone, in contrast to these four 2001 Hawaii isolates.

The fact that the four 2001 Hawaii isolates had the same antibiograms and the same strain type suggests that a single multidrug-resistant strain with decreased susceptibility to cefixime was identified in Hawaii in the spring of 2001. How the

strain appeared in Hawaii is unclear; the inability to obtain additional information on other sex partners limits the investigation, but the links to sex partners from Asia, particularly Japan, is intriguing and suggests that Asia may again be a source of new antimicrobial resistance for *N. gonorrhoeae.*

In 1999, six patients in Kitakyushu, Japan, were identified as having gonococcal infections that had antimicrobial susceptibility patterns (β-lactamase negative; MIC of penicillin, 4.0 mg/L; MIC of tetracycline, 4.0 mg/L; MIC of cefixime, 0.25–0.5 mg/L; MIC of ceftriaxone, 0.125 mg/L; and MIC of ciprofloxacin of 2.0–64.0 mg/L) similar to the susceptibility patterns of the 4 Hawaii isolates [20]. Similar strains were identified during 2000–2001 in Kitakyushu, Yamaguchi, and Tokyo [21], suggesting ongoing transmission. Of note, several patients who were infected with these strains and treated with cefixime (400 mg q.d. for 3 days) were reported to have had cefixime treatment failures [22].

With the ongoing spread of infection with resistant *N. gonorrhoeae* strains, clinicians need to routinely obtain the travel history for patients suspected of having gonorrhea so that appropriate antibiotics may be selected for treatment [9]. Clinicians who suspect or identify a gonorrhea treatment failure should submit a gonococcal culture specimen to the appropriate local laboratory for susceptibility testing. When a patient receives a diagnosis of *N. gonorrhoeae* infection that is resistant to CDC-recommended treatment, it is also important for the patient's sex partners to be identified, tested, and treated, so that ongoing transmission of resistant *N. gonorrhoeae* is prevented.

Because *N. gonorrhoeae* must be grown in culture for antimicrobial susceptibility testing to be performed, the increasingly widespread use of non–culture-based diagnostic tests poses a significant challenge to monitoring antimicrobial resistance. Local capacity to perform gonococcal culture is necessary to generate local susceptibility data, because prevalence of gonococcal resistance varies considerably by location. Furthermore, surveillance for gonorrhea treatment failures alone is inadequate to detect resistance in *N. gonorrhoeae,* because gonorrhea is asymptomatic in ~80% of infected women and at least 10% of infected men. Ongoing gonococcal susceptibility surveillance to describe the local prevalence of resistance will continue to be crucial for the successful treatment and control of gonorrhea.

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